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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
07/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,943	MCMICHAEL ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *8,9,11,13,17-26,29-31,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,10,12,14-16,27,28,32 and 33* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 May 2008 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

DETAILED ACTION

Claims 1-35 are pending. Claims 8, 9, 11, 13, 17-26, 29, 30, 31, 34 and 35 are withdrawn. Claims 1-7, 10, 12, 14-16, 27, 28, 32 and 33 are pending and currently examined.

Claim Objections

The objection to claim 5 is maintained for reasons of record.

Double Patenting

The statutory rejection under 35 U.S.C. §101 of claims 45-52 and 56-61 as claiming the same invention as that of claims 35, 37-45 and 48-51 of US Patent No. 6,737,066 B1 is **withdrawn**.

The nonstatutory double patenting rejection of claims 1-6, 10, 14-16, 27 and 31-33 as being unpatentable over claims 1,2, 5-7, 15-18, and 20 of U.S. Patent No. 6,663,871 will be withdrawn upon Applicants' submission of a compliant terminal disclaimer.

The provisional nonstatutory double patenting rejection of claims 1-3, 6, 7, 10, 12, 14 and 15 as being unpatentable over claims 1,4, 5, 9, 11, 13 and 14 of copending Application No. 10/833,439, of claims 1-3, 6, 7, 10,. 12, 14 and 15 as being unpatentable over claims 1,4, 5, 9, 11 and 13-16 of copending Application No. 10/833,744, of claims 1-3, 5-7, 10, 12, 14 and 15 as being unpatentable over claims 1,4, 5, 9, 11, and 13-15 of copending Application No. 10/833,745, and of claims 1, 6 and 27

as being unpatentable over claims 1-5 and 6-8 of copending Application No. 10/653,624 are held in abeyance until allowable subject matter is determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-4, 6, 7, 10, 12, 14-16, 27, 28, 32 and 33 under 35 U.S.C. §103(a) as being unpatentable over Li *et al.* (1993, reference No. AU4 in IDS filed on 06 July 2004) in view of Sutter *et al.* (1992, reference No. C52 in IDS filed on 09 November 2006) and Stoute *et al.* (January 1997) is **maintained.**

The instant claims are directed to a method for generating a $CD8^+$ T cell immune response in a mammal against at least one target antigen such as malaria, comprising administering to said mammal at least one dose of each of the following:

(i) a priming composition comprising a replicating viral vector expressing one or more $CD8^+$ T cell epitopes of the target antigen; and

(ii) a boosting composition comprising a non-replicating or replication-impaired recombinant virus vector expressing one or more $CD8^+$ T cell epitopes of the target antigen, including at least one $CD8^+$ T cell epitope, which is the same as a $CD8^+$ T cell epitope of the priming composition; with the proviso that the viral vectors in (i) and (ii) are derived from different viruses.

Li *et al.* describe priming with recombinant influenza virus followed by boosting with recombinant vaccinia virus induces $CD8^+$ T-cell-mediated protective immunity against malaria. The sequence of immunization appears to be crucial, since a primer injection with recombinant vaccinia virus, followed by a booster injection with recombinant influenza virus, failed to induce protection. The protection induced by immunization with these recombinant viruses is mostly mediated by $CD8^+$ T cells. See abstract. Suggested routes of administration were i.p., by aerosol, and intravenous injection. See p. 5215, left column.

Li *et al.* do not describe a replication-impaired or non-replicating recombinant virus vector in the boosting composition and an adjuvant.

Sutter *et al.* describe a non-replicating vaccinia vector, modified vaccinia Ankara (MVA) strain that has been safety tested in humans. See Abstract.

Neither Li *et al.* or Sutter *et al.* suggest an adjuvant of SBAS2.

Stoute *et al.* describe malaria vaccine formulations in three kinds of adjuvants: alum and monophosphoryl lipid A (SBAS4), an oil-in-water emulsion (SBAS3), and an oil-in-water emulsion plus the immune stimulants monophosphoryl lipid A and QS21 (SBAS2). The vaccines were administered intramuscularly. See p. 87, Study Design and Vaccines. Stoute et al. further describe that SBAS2 is the most efficacious adjuvant. See p. 90, Discussion.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the priming and boosting compositions of Li *et al.* so as to replace the replicating vaccinia vector with a safer non-replicating MVA vector as taught

by Sutter *et al.* One having ordinary skill in the art would have been motivated to do this because a live vaccinia virus is infectious while MVA does not replicate in mammalian cells yet expresses recombinant genes efficiently, as suggested by Sutter *et al.* It would have also been obvious to one of ordinary skill in the art at the time the invention was made to add the SBAS2 adjuvant, as taught by Stoute *et al.*, to the priming and boosting compositions of Li *et al.* One having ordinary skill in the art would have been motivated to do this because SBAS2 may also provide signals required to up-regulate co-stimulatory molecules on antigen-presenting cells, induce expression of molecules that permit these cells to travel to target tissues, or induce production of cytokines that mediate protection, as per suggested by Stoute *et al.* There would have been a reasonable expectation of success, given the results that the SBAS2 formulation proved superior for inducing strong antibody responses and strong antigen-specific delayed hypersensitivity in primates and for inducing proliferative and cytolytic T cell responses in mice, as taught by Stoute *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 15 May 2008 have been fully considered but they are not persuasive. Applicants argue that:

1) The Mackett Declaration and the teachings of Reference AT8 indicate that there was a clear bias in the art at the time of the invention towards using replicating viral vectors for immunization;

2) Li *et al.*'s teaching of the "remarkable synergistic effect" of using the specific combination of a recombinant influenza virus prime and replicating recombinant vaccinia virus boost in their immunization method to induce $CD8^+$ T cell-mediated protective immunity against malaria discourages one skilled in the art from modifying their successful immunization method;

3) Sutter *et al.* do not teach or suggest that immunization with their MVA vector can elicit a $CD8^+$ T cell response in a mammal; and

4) Sutter *et al.* fail to demonstrate that MVA is able to synthesize high levels of a foreign protein in vivo in human cells, or that MVA can be safely used to immunize humans or other mammals.

In response to Applicants' four points of argument, Examiner respectfully submits the following reasoning:

Applicants' assertion that the opinion of those of skill in the art, including Dr. Mackett's declaration, is to use replicating viral vectors for immunization in the art at the time of the invention is not convincing. Such an opinion could be due to concerns of inefficient expression of the antigens before the discovery of a more efficient expression vector. The opinion fails to set forth any facts purporting to be objective evidence. To be of probative value, any objective evidence should be supported by actual proof. Applicants have not presented any experimental data showing that the replicating vaccinia virus has more $CD8^+$ T cell boosting effect than the suggested MVA vector. The mere "bias towards replicating virus vector" in the art at the time of invention would

not deter one skilled in the art from making modification to immunization methods as new and safer virus vectors are discovered.

With regards to the Li reference, the mere "synergistic effect" of the heterologous prime-boost immunization method does not prevent one skilled in the art from modifying Li's immunization method for improved safety in humans. Applicants' opinion that the success of one immunization method prevents one skilled in the art from modification lacks evidentiary basis.

The Sutter reference was offered for teaching the claimed non-replicating or replication-impaired virus vector. Even though Sutter *et al.* are silent on the type of elicited immune response, MVA is still a modified vaccinia virus that efficiently expresses the antigens, in this case, the $CD8^+$ T cell epitopes, which induces the antigen-specific $CD8^+$ T cell response. Applicants have not presented actual proof or scientific reasoning to show that an MVA vector expressing $CD8^+$ T cell epitopes would not elicit $CD8^+$ T cell response.

Furthermore, Sutter *et al.* clearly provides the motivation for one skilled in the art to substitute a recombinant vaccinia virus with the replication-impaired vaccinia virus, MVA, because of its non-replicativity and thus safety in mammals yet high efficiency in expressing foreign proteins that can be antigens like $CD8^+$ T cell epitopes in human cells (page 10847), which negates Applicants' argument that Sutter *et al.* fail to demonstrate that MVA is able to synthesize high levels of a foreign protein *in vivo* in human cells. Applicants' assertion of the MVA safety in humans and other mammals lacks evidentiary basis.

Applicants also argue that the alleged motivations are not mentioned in the cited references. This is not the standard. The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

Thus, the combination of Sutter *et al.* and Li *et al.* is properly motivated and a *prima facie* case of obviousness is properly established.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
8 July 2008

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648